Charles University
Faculty of Science

Study programme: Biology
Branch of study: Biology

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Role of the hippocampal-neocortical interplay during the memory retrieval
Role hipokampálně-neokortikálních interakcí ve vybavování paměti

Bachelor´s thesis

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Prague, 2021

Poděkování:

Ráda bych poděkovala svému školiteli prof. RNDr. Aleši Stuchlíkovi, DSc. za pomoc, kterou mi během psaní této práce poskytl.

Prohlášení:

Prohlašuji, že jsem tuto závěrečnou bakalářskou práci zpracovala samostatně a že jsem uvedla všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

V Praze dne 5. 5. 2021,

Podpis:

Abstract

The hippocampus is undoubtedly a fundamental structure for the proper function of declarative memory, which is divided into episodic, semantic, and possibly also spatial memory. The internal hippocampal connectivity includes two pathways - the direct pathway from the entorhinal cortex to CA1, and the indirect trisynaptic pathway beginning in the entorhinal cortex, traversing through the subiculum and dentate gyrus further to CA3 and CA1. Both these pathways eventually end again in the entorhinal cortex. This cortex is thought to be the main interface between the hippocampus and the neocortex as it is the main source of projections to the neocortex. The neocortex, which forms the greatest part of the cerebral cortex, is connected to the hippocampus via many structures and mechanisms. Their interaction through neocortical areas, as the prefrontal and parietal cortices, is important not only for memory retrieval but also for other cognitive processes. These mechanisms include CA1 backprojections to the entorhinal cortex and the parahippocampal gyrus eventually ending in the neocortex, furthermore, the neuronal reinstatement, neural theta rhythm as well as gamma oscillations. The reactivation of engram cells is also playing a key role as it might induce memory retrieval and further research may lead to an effective strategy for treating memory impairment in Alzheimer's disease. How the hippocampal system works including the connections with other parts of the brain is still widely researched. During encoding, the interaction between the prefrontal cortex and hippocampal region provides long-term storage of information in memory. Their cooperation during memory retrieval specifies cues of retrieval, monitors, and reactivates stored knowledge.

Key words: memory trace; animal model; hippocampus; cortical reinstatement; memory

Abstrakt

Hippocampus je nepochybně základní strukturou pro správnou funkci deklarativní paměti, která se dělí na epizodickou, sémantickou a případně i prostorovou. Interní hipokampální konektivita zahrnuje dvě dráhy – přímou cestu z entorhinální kůry do CA1 a nepřímou trisynaptickou cestu začínající v entorhinální kůře, procházející skrze subiculum a gyrus dentatus dále do CA3 a CA1. Obě tyto dráhy nakonec končí opět v entorhinální kůře. Tato kůra je považována za hlavní rozhraní mezi hipokampem a neokortexem a je hlavním zdrojem projekcí do neokortexu. Neokortex, který tvoří největší část mozkové kůry, je spojen s hipokampem prostřednictvím mnoha struktur a mechanismů. Jejich interakce skrze neokortikální oblasti, jako prefrontální a parietální kůry, je důležitá nejen pro vybavování paměti, ale také pro další kognitivní procesy. Mezi tyto mechanismy patří zpětné projekce CA1 do entorhinální kůry a parahippocampálního gyru končící v neokortexu, dále neurální znovuustavení, theta rytmus a také gama oscilace. Reaktivace engramových buněk také hraje zásadní roli, jelikož by mohla vyvolat vybavení paměti a další výzkum může vést k účinné strategii léčby poruchy paměti u Alzheimerovy choroby. Jak hipokampální systém funguje, včetně jeho spojení s jinými částmi mozku, je stále intenzivně studováno. Interakce mezi prefrontální kůrou a hipokampální oblastí během kódování poskytují dlouhodobé uložení informací do paměti. Jejich spolupráce při vybavování vzpomínky specifikuje vybavované podněty, monitoruje a znovu aktivuje uložené vzpomínky.

Klíčová slova: paměťová stopa, zvířecí model, hipokampus, korové ustavování, paměť

List of abbreviations

CA (CA1, etc.)	Cornu Ammonis
EEG	electroencephalography
fMRI	functional magnetic resonance imaging
GABA	gamma-aminobutyric acid
HPC	hippocampal
iEEG	intracranial electroencephalography
LFPs	local fields potentials
mPFC	medial prefrontal cortex
MAR model	the Memory as Reinstatement model
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
MTL	medial temporal lobe
PET	positron emission tomography
PFC	prefrontal cortex
PPC	posterior parietal cortex

Contents

1 Introduction

Memory is an integral part of an animal´s life and is usually defined ability to encode, store and retrieve information when needed. It retains acquired knowledge or experiences over time to influence future actions. Santiago Ramon y Cajal (1894) in his Croonian lecture in England predicted that learning could be mediated by changes in the connections between individual nerve cells (discussed by Jones, 1994). The common belief is that the first hypothesis suggesting a direct role of neurons (nerve elements) for memory functions was proposed in 1881 by Théodule-Armand Ribot, a French philosopher and psychologist, who came with the idea that "memory is, in essence, a biological fact and, accidentally, a psychological fact" (Nicolas et al., 2016). Many different types of memory exist. Apart from division into sensory memory, short-term and long-term memory (based on the time course of memory), it is often divided into two main categories (based on the nature of the information that is stored): declarative memory (learning of ''what'') and procedural memory (learning of ''how''). Declarative memory is further divided into episodic memory - memories of specific events and experiences (containing the "what", "when" and "where" aspects), and semantic memory - memories of facts (Paller, 2009). It is currently a matter of debate whether spatial memory should be included as a specific subtype of declarative memory. Remembering of declarative memories involves the conscious or explicit retrieval of information about specific experiences. The recovery of stored information from the long-term memory, the memory retrieval, is a feature of virtually all cognitive activity. It consists of the resulting firing of appropriate output units (Graf & Schacter, 1985; Lockhart, 2001). The "tool" mediating this process in the case of declarative memories is the hippocampal region, a unique C-shaped brain structure playing a crucial role in declarative, especially episodic, and spatial memory systems (Amaral & Witter, 1989; Witter & Groenewegen, 1990). The interplay of the hippocampus with the neocortex, the largest part of the cerebral cortex, contributes to successful memory retrieval. The evidence that the prefrontal cortex (PFC), an interconnected set of neocortical areas, and the hippocampus interact has been demonstrated in numerous studies for example by disconnecting these areas. These disconnection analyses showed that PFC–hippocampal interactions are required for object–place associative discriminations (Barker et al., 2007), and lesions in the PFC can also disrupt episodic memory (Duarte et al., 2005). There is also direct evidence of functional interaction between the hippocampus and medial PFC (mPFC) required for the retrieval of episodic memory in rodents (Barker et al., 2017). PFC is also activated during the retrieval of semantic memory (Demb et al., 1995). The role of the posterior parietal cortex (PPC) in the retrieval process has been emphasized as well (Jonides et al., 1998; Konishi et al., 2000). In non-human mammals, encoding and retrieval of the so-called episodic-like memories are important for their survival. These animals can build a higher-order memory for unique events comprising information about what, where, and when (Clayton & Dickinson, 1998; Dere et al., 2005).

Several mechanisms are considered essential for declarative memory retrieval. Many studies suggest that the hippocampus–mPFC interactions are mediated by information transfer from the

hippocampus to the mPFC via the direct projections from hippocampal CA1 subfield to mPFC (Barker et al., 2017; Rolls, 2016). The neural reinstatement is also recognized as a mechanism contributing to successful memory retrieval as when remembering an event, the information obtained (encoded) in that memory is represented across the brain. The retrieval of this information allegedly involves the reinstatement of those representations (Teyler & DiScenna, 1986; Teyler & Rudy, 2007; Davachi & Danker, 2013). Another idea relates to memory traces, engrams, which are stabilized by neuronal reactivation involved in memory consolidation. This subsequent reactivation of engram cells induced by various cues present during the event enhances the retrieval of memories (Roy et al., 2016; Kitamura et al., 2017; Tonegawa et al., 2018; Pignatelli et al., 2019). Considerable evidence has emerged that PFC–hippocampal interactions during episodic memory tasks are mediated via oscillatory synchrony of neural activity in these regions, specifically of theta oscillations (3–12Hz) playing a mechanistic role in the retrieval process (Givens, 1996; Hasselmo et al., 2002; Jones & Wilson, 2005). There is wide agreement that extrahippocampal projections contribute to the formation of theta oscillations as well as to the function of the hippocampal-neocortical circuits (Herkenham, 1978; Smythe et al., 1992; Konopacki & Gołebiewski, 1993; Varela et al., 2014).

This thesis will deal with the basic types of declarative long-term memories, their neural correlates, and interactions between brain circuits of the hippocampus and neocortex that are thought to mediate them.

2 Declarative memory

Declarative (or explicit) memory is described as a conscious intentional recollection of previous experiences. It includes various forms of nonconscious memory that can be dissociated from other types of memory expression and is impaired in amnesia (McKee & Squire, 1993). In other words, it means the ability to consciously recall specific items in memory and then to express the recalled memory of a learned fact or past experience in a variety of ways, mainly verbally (McKee & Squire, 1993; Eichenbaum, 1997). Declarative memory comprises both episodic and semantic memories which are promoted by the hippocampus and associated with the temporal and frontal neocortex (Digiulio et al., 1994; Paller, 2009). The medial temporal lobe (MTL) comprises several structures, including the hippocampal and surrounding cortices (parahippocampal cortex, entorhinal cortex, and perirhinal cortex), which contribute differently to declarative memory. Declarative memory relies on the integrity of these structures (Preston et al., 2004).

An interesting form of memory worth mentioning is prospective memory, which refers to the ability to plan and later retrieve an intention at a specific future point. This type of memory is important in everyday life because it allows us to structure our time effectively. The social importance, which is linked to motivation, should facilitate the encoding and storage of an intention in the memory system.

Motivation might improve the likelihood of prospective remembering (Brandimonte et al., 1996; Cicogna & Nigro, 1998).

2.1 Episodic memory

Episodic memory is a memory system that receives and stores information about temporally dated episodes or events, as well as relations among these events in the context of time and space (Tulving, 1972). It is especially vulnerable to neuronal dysfunction (Goldblum et al., 1998). This system allows one to time travel mentally from the present to the past and allowing one to consciously remember one's own previous experiences. This process is assumed to be unique for humans (Tulving, 2002). A particular event is always stored when it refers to the already stored existing contents of the episodic memory. Memories can be stored solely in terms of their perceptible attributes. The retrieval process of this information as well as making the retrieved knowledge accessible is also a special type of input into episodic memory and consequently changes the contents of the episodic memory storage. The episodic system can operate relatively independently of the semantic system. However, the specific way how the perceived input is registered can be strongly influenced by information in semantic memory (Tulving, 1972).

Unlike humans, animals are not capable to give a verbal description of personal past experience, which would prove their conscious recollection and re-experience of an event. Nevertheless, there are situations where an animal's ability to recall specific information from the past is important for its survival. Non-verbal animals may instead possess an implicit form of episodic memory, enabling the ability to remember and to build a higher-order memory for unique events comprising information about what, where, and when. Because of the absence of behavioral evidence of autonoetic consciousness (the ability to mentally time-travel), it is not considered to be part of episodic memory, but it is distinct from other demonstrations of declarative memory in animals, and therefore the term "episodic-like" memory was introduced (Clayton & Dickinson, 1998; Dere et al., 2005).

Episodic memory has some other important properties, such as encoding of experienced events occurring sometimes automatically. It means that the system cannot be simply "turn off" by just a decision of one's own free will (Martin et al. 1997; Morris & Frey, 1997). An example of this "reflexive" characteristic is witnessing a car accident during a routine activity such as grocery shopping. It automatically becomes impossible not to encode and rapidly remember that the accident happened and where and when it happened. The witness can remember the scene, the crash itself, what happened immediately afterward, and anything else unusual (Morris, 2006).

2.2 Semantic memory

The distinction between episodic and semantic memory was first described by Endel Tulving (1972). Semantic memory is a memory system enabling recollecting of facts and general knowledge about the world that are context-free e.g., the name and color of a banana. These memories are typically retrieved automatically. Episodic memory, on the other hand, refers to the capacity to re-experience a single event in the specific context in which it occurred, as previously mentioned above. Unlike semantic, it requires conscious recollection e.g., "I ate a banana at lunch yesterday" (Wiggs et al., 1999; Manns et al., 2003). Semantic memory is also necessary for the use of language. This type of memory includes organized knowledge about words and other verbal symbols, as well as knowledge about the relation between words and sentences, assigning them their proper meaning. It also provides information about the rules and manipulation manuals for these concepts and relations. The semantic system permits the retrieval of information that was not directly stored in it. The retrieval from this system leaves its contents unchanged, thus it is much less susceptible to unwanted changes and loss of information than the episodic one. It should be kept in mind, that any retrieval act requires input into episodic memory, however, it is commonly believed that this system can be independent of the episodic system in recording and maintaining information as storage of semantic knowledge can be achieved by a wide range of input signals (Tulving, 1972). Until recently, it was not completely known whether the hippocampus played an important role only in episodic memory or in semantic memory too. The answer came from results, which showed that hippocampal areas support both those types – semantic and episodic memory, but its role in acquiring and storing semantic information is presumably limited in time (Manns et al., 2003).

2.3 Spatial memory

There is a wide agreement that the hippocampus is required for spatial memory, which enables spatial navigation in animals such as rats. Rats have a remarkable memory capacity for spatial information. It is visible in situations in which a simple sensory stimulus or a well-learned path is not enough to solve the task (Olton & Samuelson, 1976; Morris et al., 1982; Pearce et al., 1998). Rodent hippocampus is necessary for the animal to be able to avoid a moving target, however, not to avoid a stable one (Telensky et al., 2011). Results of King's studies point to a close relationship between the mechanisms of episodic and spatial memory, in which the hippocampus is playing a key role. This role seems to require storing context-rich memories in a form permitting both the identification of a familiar place from a novel viewpoint as well as the reconstruction of a viewpoint-specific experience concerning past events (King et al., 2004). Apart from the hippocampus, the mPFC together with other cortical areas may contribute largely to spatial cognition as well as to retrieval of spatial memory in rats (Baker et al., 2007; Jo et al., 2007, Cholvin et al., 2016).

The place cells, discovered by O´Keefe and Dostrovsky (1971), are a type of pyramidal neurons crucial for spatial memory as they form a map of a particular given environment. This information was confirmed very recently by Robinson and colleagues showing the causal role of place cells and spatial navigation. The optogenetic stimulation of place cells changes the animal behavior in a maze (Robinson et al., 2020). A model was described by O'Keefe, who suggested that each cell represents a part of that environment and receives two different inputs. The first input conveys information about environmental stimuli or events, and the second input forms a navigational system by calculating the exact position of the animal in an environment independently of the stimuli. Inputs from the navigation system prevent inputs from the environment allowing only those stimuli that occur when the animal is in a specific place to excite the specific place cell (O'Keefe, 1976).

Studies from the first decade of the 21st century by the laboratory of Edvard and May-Britt Moser from Trondheim indicate that the entorhinal cortex is significantly involved in the recognition of space and time. Their results describe the spatial firing patterns of principal neurons, the grid cells, in the medial entorhinal cortex (Hafting et al., 2005). Each grid cell has multiple firing fields organized in a periodic hexagonal lattice across the surface of an environment. These cells are possibly part of a generalized map of the spatial environment, possibly providing metrics for the space even in the absence of visual information (Fyhn et al., 2004; Hafting et al., 2005, Moser et al., 2008). There are also other types of spatially-tuned cells in the limbic system and associated areas as the head direction cells (Taube et al., 1990), border cells (Solstad et al., 2008), boundary-vector cells (Hartley et al., 2000). Intriguing types of spatially selective cells are found in mammals navigating in 2D space, such as bats in Ulanovsky´s work on vector goal cells (Sarel et al., 2017). It is noteworthy that John O´Keefe and Edvard and May-Britt Mosers were awarded the Nobel Prize in 2014 for these discoveries.

Each head-direction cell fires rapidly only when the head of a moving rat points in a restricted range of angles in the horizontal plane. The firing rate appears to depend only on the angle between the midline of the head and a reference direction. The preferred direction is constant over the entire area of the recording chamber and thus the vectors in the direction of maximal firing are everywhere parallel. It is therefore clear, that the head-direction cells share with hippocampal place cells the ability of signaling an aspect of the spatial relationship between the animal and its environment (Taube et al., 1990).

The border cells are an entorhinal cell type that fires when an animal is close to the borders of the proximal environment, and thus defines the perimeter of the environment. Border cells could serve as reference frames for place representations within that environment, determining the firing locations of place cells in the hippocampus and other spatially selective cells (Solstad et al., 2008). It is assumed that place cells receive inputs from many boundary vector cells, which collectively cover the whole range of boundary vectors that the rat can ever encounter (Hartley et al., 2000) and thus contribute environmental information to place cell firing, complementing path integrative information (Lever et al., 2009). For example, when the rat encounters a wall, the firing rate of boundary cells increases (Hartley et al., 2000).

3 Hippocampal region – the hippocampus and its related parts

The hippocampal region comprises the hippocampal formation and the parahippocampal region. The hippocampal formation is a functional system referring to a group of relatively simple cortical regions including the dentate gyrus, the hippocampus proper (CA1, CA2, and CA3 subfields), sometimes termed as the Ammon's horn, the subicular complex, which is divided into the subiculum, presubiculum, and parasubiculum, and finally, the entorhinal cortex, which is generally divided into medial and lateral subdivisions used particularly when referring to the rodent brain. There is no clear consensus on which areas of the brain this term covers. The rodent hippocampal formation has a relatively complex three-dimensional shape, and it appears grossly as a bilateral elongated structure. Its long axis generally called the septotemporal axis, bends in a C-shaped manner from the septal nuclei rostro-dorsally to the incipient temporal lobe caudo-ventrally. The orthogonal axis can be referred to as the transverse axis (Amaral & Witter, 1989; Witter & Groenewegen, 1990).

The hippocampus plays a critical role in memory for all kinds of relations. This information is known since the loss of recent memory after bilateral hippocampal lesions of patient H.M. - Henry Gustav Molaison (1926 - 2008). Studies of this patient showed that the hippocampus together with associated MTL structures are critical components of a functional system for long-term memory formation (Scoville & Milner, 1957). The hippocampus is a cortex, occasionally referred to as the archicortex. The parahippocampal gyrus is a grey matter surrounding the hippocampus, which receives input from all areas of the cerebral cortex (Paller, 2009).

3.1 Hippocampus proper

The term hippocampus proper refers to the actual structure of the hippocampus made up of several subfields. Lorente de Nó (1934) divided the hippocampus into three subfields: CA3, CA2, and CA1. The abbreviation CA comes from Cornu Ammonis (horn of Egyptian mythology god Ammon). He defined the CA2 field as containing cells similar in size to those in CA3, but unlike those, the CA2 cells are not innervated by the mossy fibers. He also divided field CA1 into three parts (CAla, CAlb, and CAlc); however, recent studies do not consider this division to be accurate (Ishizuka et al.,1990).

The CA fields of the hippocampus can be subdivided into several layers, from the ventricular to pial surfaces to the alveus, stratum oriens, stratum pyramidale, stratum lucidum, which is the mossy fiber layer of the CA3 field, stratum radiatum, and stratum lacunosum-moleculare. These layers differ in the sublaminar distribution of intrahippocampal projections (labeled fibers) originating from different parts of the CA3 with a different location of the CA3 cells in the transverse axis. Studies indicate that projection patterns change gradually when proceeding from the CA3 cells located closest to the dentate gyrus to those cells located adjacent to the CA2 field. It was discovered that the CA2 field can be also distinguished from CA3 by the pattern of its intrinsic connections. These differences in connectivity as

well as the lack of mossy fiber input support its designation as a separate hippocampal field. The majority of the associational connections of the CA3 cells are from the deep parts of the stratum radiatum (Ishizuka et al.,1990).

3.2 Entorhinal cortex

The area of the entorhinal cortex, which occupies a pivotal position within the hippocampal formation, is interposed between the neocortex on one side and the dentate gyrus with the hippocampal subfields on the other. This structure is generally divided into six main subdivisions based especially on cytological aspects (Amaral et al., 1987). It can be also divided into two main parts - the classical lateral and medial entorhinal areas, which are later subdivided (van Groen et al., 2003). One of the most significant differences between the entorhinal cortex and most neocortical fields is the absence of a characteristic internal granular layer. The small, densely packed stellate neurons characterizing layer IV throughout most of the neocortex, are replaced, in the entorhinal cortex, by a dense bend of fibers in a corresponding zone (Amaral et al., 1987). Two nomenclatures of cortical lamination may be applied to the entorhinal cortex. The first, proposed by Ramón y Cajal (1902, 1911), divide the entorhinal cortex into seven layers. As stated in this scheme, there are four cellular layers (II, III, V, and VI) and two acellular layers (I and IV). The six-layered second scheme suggested by Lorente de Nó (1933) includes 5 cellular layers (II, III, IV, V, VI) with a cell-free lamina dissecans (layer IIIb) between layers III and IV. The whole structure in the human brain occupies an area several centimeters in size situated over the gyrus ambiens and parahippocampal gyrus in the middle of the medial temporal region (Krimer et al., 1997).

Witter and Amaral's studies showed that in primates and non-primates, the entorhinal cortex prominently projects to the molecular layer of the dentate gyrus, to the stratum lacunosum-moleculare of all hippocampal subfields, and to the molecular layer of the subiculum. The projection to the dentate gyrus and to the CA3 and CA2 fields arise mainly from cells located in layer II, but also from the cells of layer VI, in contrast with projection to CA1 and subiculum, which is formed primarily from cells in layer III and less from layer V (Witter & Amaral, 1991). It was confirmed that the lateral entorhinal area projects also to all parts of the olfactory cortex, cingulate gyrus, medial prefrontal region, and perirhinal regions (Swanson & Köhler, 1986).

3.3 Dentate gyrus

The dentate gyrus has unique neuroanatomy with three layers comprising a relatively cell-free molecular layer occupied by a small number of interneurons and fibers from a variety of extrinsic inputs terminating there, and also by the dendrites of the dentate granule cells. The major afferents are the perforant path fibers originating in the entorhinal cortex. Three of the most important neurons in the dentate gyrus are the dentate granule cells, the dentate pyramidal basket cells, and the mossy cells. The second layer is the principal-granule cell layer, made up mainly of densely packed granule cells. The

third polymorphic cell layer is where many cell types including the most eminent, mossy cells, are situated (Amaral et al., 2007). Granule cells are critically placed and optimized to relay input from the entorhinal cortex into the hippocampus proper and the dendritic integration in these cells is necessary for the processing of this synaptic input (Krueppel et al., 2011).

To distinguish similar episodes, the hippocampus minimizes overlap of the similar representations at the time of storage assigned to different cortical patterns. This process is termed pattern separation and is performed via the feedforward pathway from the entorhinal cortex to the dentate gyrus and to the CA3. Specific episodes are usually not replicated in full form as the recalled pattern reflects a considerable loss of detail and increased noise relative to the original. Consequently, the hippocampus must also be able to use partial cues for the retrieval of previously stored representations and then respond appropriately. This process is called pattern completion and is likely performed via the recurrent and auto-associative highly plastic network in the CA3 (O'Reilly & McClelland, 1994; McClelland & Goddard, 1996). The fact that the dentate gyrus is very important for the ability to successfully discriminate between similar contexts is shown in the experiment with transgenic mice lacking an essential subunit of the N-methyl-D-aspartic receptor NR1 in dentate granule cells, which performed normally during a contextual fear conditioning task but were not able to distinguish between the fear conditioning context and a novel similar context (McHugh et al., 2007). The dentate gyrus is one of the few areas where neurogenesis in humans and rodents continues throughout life (Altman, 1962, 1963; Kuhn et al., 1996, Eriksson et al., 1998).

3.4 Subiculum

It is believed that the subiculum, through its divergent efferent projections, plays a key role as a link in the communication between the hippocampus and the rest of the brain. The information processing along the trisynaptic circuit (see below) is relayed via the subiculum to a wide range of cortical and subcortical areas, including the entorhinal cortex. The efferents leave the subiculum by two paths: a dorsal path via the fimbria-fornix system and a ventral path via the angular bundle and the entorhinal cortex. All of these leaving axons innervate partly different structures, although certain overlap is possible (Köhler, 1990). The subiculum is the final stopping point in what is considered a largely unidirectional sequence of projections in the hippocampus circuitry, which connects the various subdivisions of the hippocampus. It is a heterogeneous structure, considering its efferent and afferent connectivity (Witter & Groenewegen, 1990). The subiculum also creates a projecting pathway to the hypothalamus (Kishi et al., 2000). There are different opinions as to whether the area between CA1 and the subiculum, the prosubiculum, exists. Generally, the subiculum is bordered distally by the presubiculum which is bounded equally by the parasubiculum, and the latter area of the subiculum adjoins the entorhinal cortex (Witter & Groenewegen, 1990).

3.5 Neocortex

The neocortex is a critically important organ for consciousness and other higher-order brain functions. The six-layered neocortex is the largest part of the human cerebral cortex, which is the outer layer of the cerebrum (Noback et al., 2005). From the point of view of declarative memory, it is appropriate to focus mainly on neocortical association areas.

The prefrontal cortex (PFC) and the posterior parietal cortex (PPC) are two neocortical regions described as crucial to memory function, apart from the hippocampus. The PFC is the cerebral cortex covering the front part of the frontal lobe. Within the human PFC, two different regions can be distinguished morphologically and evolutionarily - the ventromedial PFC comprising the ventral PFC and the medial PFC present in mammals, and the lateral PFC, consisting of the dorsolateral PFC, which in humans corresponds to medial PFC (mPFC) in rats, and the ventrolateral PFC, present only in primates (Kaas, 1990; Kolb, 2010, Noback et al., 2005). PPC and PFC are associative cortical regions, as they combine inputs from many brain areas e.g., somatosensory, motor, cingulate, and prefrontal cortices, and then integrates signals from subcortical areas. The anterior parietal cortex in humans involves primary somatosensory areas, whereas the PPC has higher-order functions such as coding for some aspects of space (Whitlock, 2017).

The precuneus, posterior cingulate cortex, and retrosplenial cortex are other cortical areas, which are especially important for consciousness. The human posterior cingulate cortex and retrosplenial cortex form the posterior cingulate gyrus (Vogt et al., 2006; Wang et al., 2019). The retrosplenial cortex receives its main inputs from the hippocampal formation, the parahippocampal cortex, and the frontal lobe (frontal part of the neocortex), mainly area 46, which corresponds with the dorsolateral PFC. The posterior cingulate cortex receives its main inputs from the parietal and occipital visual cortices and from the frontal lobe (Kobayashi & Amaral, 2003).

3.6 Intrinsic connectivity of the hippocampus

There are two main excitatory circuits involving the entorhinal cortex and hippocampal networks: the direct pathway and the indirect pathway. The first one, the direct pathway, is arising from entorhinal cortex layer III, traversing to the hippocampal CA1 field, and later returning to the entorhinal cortex to layer V. The second one is the indirect trisynaptic pathway, arising from entorhinal cortex layer II passing through the dentate gyrus, then traveling to the hippocampal CA3 field, which is projecting to the hippocampal CA1 field, and finally terminating in the entorhinal cortex layer V (Andersen et al., 1971; Rolls, 2016).

3.6.1 Trisynaptic circuit

The internal circuitry of hippocampal regions is shown in Fig. 1. This generally accepted hippocampal circuitry has been studied by numerous authors. The perforant pathway projections from

the entorhinal cortex, reach the granule cells of the dentate gyrus (Andersen et al., 1971). These granule cells project via their mossy fibers to pyramidal cells of the CA3 field, which in turn give rise to axons of the Schaffer-collaterals providing the major input to CA1. Pyramidal cells in CA1 can also project to the subiculum. This projection then can reach from the subiculum to the anterior thalamus and the mammillary bodies (Witter & Groenewegen, 1990). The hippocampus receives inputs by the entorhinal cortex, providing extensive inputs from the neocortex. Temporal neocortical areas project to the perirhinal cortex (area 35), or the parahippocampal gyrus, which in turn projects to the entorhinal cortex (Van Hoesen & Pandya, 1975; Van Hoesen, 1982; Amaral et al., 1983).

The perforant pathway originating from the entorhinal cortex is one of the most actively investigated pathways in the brain. This pathway provides the dentate gyrus with its major cortical input. Projection to the dentate gyrus originates mainly from neurons in layer II of the entorhinal cortex. The entorhinal projection to CA3, CA1, and subiculum is bilateral and arises especially from layer III neurons. Neurons in the deeper layers of the entorhinal cortex may also partially contribute to this projection (van Groen et al., 2003). The perforant path system is probably involved in relaying the cues, which initiate retrieval in the CA3 field of the hippocampus. It is hypothesized, that retrieval initiation requires a large number of inputs through associatively modified synapses, allowing even a partial cue to be sufficient, therefore a strong retrieval cue is not necessary, as the recurrent collaterals take over in the retrieval process (Treves & Rolls, 1992; Rolls, 2016).

The pathway referred to as the mossy fiber pathway is the only projection of the dentate gyrus, specifically from dentate granule cells to the CA3 field. Dentate granule cells function as a preprocessing stage by performing pattern separation. Once a mossy fiber enters the CA3 region, it has only a few collaterals. The hypothesized reason for the small number of mossy fiber connections onto a CA3 cell (about 46) is the randomizing effect on the representations set up in CA3 (Treves & Rolls, 1992; Rolls, 1989, 2013, 2016; Cerasti & Treves, 2010). This process, the pattern separation, is enabling the forming associations to be different from earlier episodic memories and so any event or episode can set up a representation different from other episodes. Because the representations in CA3 are random, many memories can be stored in these CA3 cells (Rolls & Treves, 1998; Rolls, 2016).

In general, the CA3 to CA1 projection, the Schaffer collaterals, displays thick fibers originating from CA3 pyramidal cells, which instantly ascend through the pyramidal cell layer into stratum radiatum and later lead directly to the CA1 field. This trajectory is rather applied to CA3 cells situated closest to the dentate gyrus. Upon reaching the CA1 field, these fibers continue into stratum radiatum and ramify profusely. Many of the fibers then pass through the pyramidal cell layer to enter stratum oriens. However, there is no standard path for CA3 fibers to enter the CA1 field and the fibers appear to be opportunistic by using the most expeditious pathway given their point of origin and location of densest termination (Ishizuka et al., 1990).

3.6.2 Extrahippocampal projections to other areas

Apart from the hippocampal connectivity system, there is also an extrahippocampal system (Rolls, 2016). These systems can compete for control over e.g., contextual fear, and the hippocampal system usually dominates. The ventral subiculum is critical for the hippocampal system to win this competition (Biedenkapp & Rudy, 2008). The ventral subiculum projects to the nucleus reuniens and the paraventricular nucleus of the thalamus (Witter & Groenewegen, 1990).

In relation to the interactions of the hippocampus with PFC, it is appropriate to mention the nucleus reuniens, a thalamic region, which has reciprocal connections with frontal cortices, the cingulate cortex, retrosplenial cortex, the subiculum, perirhinal cortex, and finally the entorhinal cortex. Nucleus reuniens also receives sparse inputs from the CA1 subfield and its direct projections terminate across CA1. The mPFC–hippocampal interactions depend on the function of the nucleus reuniens because its cells, with projections to both mPFC and hippocampus, may facilitate the functional interplay of these two regions. Nucleus reuniens thus attracts attention for research on learning and memory (Herkenham, 1978; Wouterlood et al., 1990; Cassel et al., 2013; Varela et al., 2014).

The medial septal nucleus is one of the septal nuclei located in the medial olfactory area of the frontal lobe (Senut et al., 1989). The three main projections from medial septal neurons to the hippocampus are GABAergic, cholinergic, and glutamatergic, and seem to be pivotal for many memory functions. It is assumed that the activity of glutamatergic neurons predicts the initiation of locomotion of mice and the future running speed (Frotscher & Léránth, 1985; Freund & Antal, 1988; Fuhrmann et al., 2015).

GABA-ergic projections from the medial septal neurons innervate most of the GABA-ergic interneurons in the hippocampus, especially in the CA3 region (Freund & Antal, 1988; Rolls, 2016). In addition to projecting to the hippocampus, the medial septum also projects to the subiculum, entorhinal cortex, and mammillary bodies (Rolls, 2016). GABA-ergic neurons can also project back to the medial septum, creating a circuit (Tóth et al. 1993; Takács et al. 2008). Both septal cholinergic and GABA-ergic afferent projections to the hippocampus are proven to be crucial for the generation of EEG theta oscillations. GABA-ergic projections reduce the overall level of inhibition by inhibiting hippocampal GABA-ergic interneurons and cholinergic projections provide the afferent excitatory drive for hippocampal theta cells. The appearance of theta synchrony in hippocampal formation requires a dynamic balance between cholinergic and GABA-ergic systems (Smythe et al., 1992; Konopacki & Gołebiewski, 1993).

4 Neocortical and hippocampal interactions in memory

Encoding and retrieval are two cardinal memory processes. Encoding receives incoming information and binds it into a memory trace as a file entry or index within the hippocampal component (Teyler & Di Scenna, 1986; Moscovitch, 1992). The retrieval process of explicit episodic memory is responsible for the interaction of cues with the memory trace, thus the memory can be recovered and delivered to consciousness. For this to happen, a memory trace must be reactivated via a cue that automatically triggers the hippocampal index (Moscovitch, 1992). Dual-process models hypothesize that this may be performed independently by recollection and familiarity processes (Tulving, 1985; Yonelinas, 1994). Recollection is assumed to be an all-or-none retrieval process, as the subject either succeeds or fails at retrieving information about that specific study event. A successful retrieval should lead to a highly confident response. Familiarity, on the other hand, is a signal detection process, whereby only items exceeding some criteria are judged as old, which is associated with the strength of the memory trace without the necessity of an additional context (Yonelinas, 1994).

For encoding and retrieval of relational information, the hippocampal-neocortical interplay is necessary. It is assumed that the hippocampus receives neocortical inputs from perirhinal, parahippocampal, and entorhinal cortices. The entorhinal cortex receives its input from perirhinal cortical areas, prefrontal neocortex, and association cortices, which are providing highly processed information from the neocortex. As mentioned in previous chapters, the entorhinal cortex has reciprocal outputs provided by the return projections (backprojections) from the hippocampus to the areas from which it receives inputs (Teyler & DiScenna, 1986; Teyler & Rudy, 2007).

Generally, the PFC has been divided into ventral and dorsal regions of lateral PFC as they are likely to be involved in different functions (Fletcher et al., 1998). As for retrieval, the ventrolateral region is thought to play a role in the controlled cue specification as well as in the maintenance of retrieved representations (Fletcher et al., 1998; Wagner et al., 2001; Dobbins et al., 2002). Dorsolateral PFC cortex, on the other hand, might be involved in the monitoring operations and selection of representations retrieved from memory and maintained by the ventrolateral frontal cortex (Fletcher et al., 1998; Rugg et al., 1999; Rowe et al., 2000; Dobbins et al., 2002).

It is suggested that the memory trace may be accessible in two ways - directly by a retrieval cue or indirectly via PFC operations. The first way, the direct retrieval, is based on the automatic cue interaction with stored knowledge in memory systems and thus the memory enters consciousness right away (Santa et al., 1975; Walker, 1986; Teyler & Rudy, 2007). During the “strategic retrieval” – the indirect retrieval, the target memory is not automatically elicited by the cue, and, therefore, must be recovered through strategic retrieval processes. The ventrolateral PFC selects the cues needed to gain access to the memory, and the dorsolateral PFC indicates that a memory search starting from those cues is needed. If retrieved

information matches the desired memory, retrieval attempts terminate (Moscovitch & Melo, 1997; Dobbins & Han, 2006; Teyler & Rudy, 2007).

In a computational model, the PFC develops and self-organizes its mnemonic codes, which serve as retrieval cues to aid retrieval from the MTL memory system (Becker & Lim, 2003). In animals, certain factors have been determined that might modulate the interaction between prefrontal and hippocampal areas, such as the time-dependent relationship between the dorsal hippocampus and the PFC in spatial memory. This study reports that the dorsal hippocampus and the mPFC process short-term spatial memory and are serving as a compensatory mechanism for each other. Results indicate that the time window of memory is a key factor in dissociating multiple memory systems and although both regions are involved, the involvement of the hippocampus may be necessary only with a sufficient delay (Lee & Kesner, 2003).

A more complicated interaction was proposed describing the role that attention plays in retrieval (Moscovitch, 1992; Dudukovic et al., 2009; Ciaramelli et al., 2008).

In addition, functional neuroimaging studies (Jonides et al., 1998; Konishi et al., 2000) presented evidence that the parietal regions also contribute to memory retrieval. Skinner and Fernandes (2007) hypothesized that areas of PPC participating in retrieval vary with different retrieval processes and different types of memory retrieved. Wagner and colleagues (2005) considered three hypotheses of the function of the PPC in memory retrieval: attention to memory representations, a mnemonic accumulator, and a memory buffer for retrieved information. This review noted that there is not much available functional neuroimaging evidence for these hypotheses.

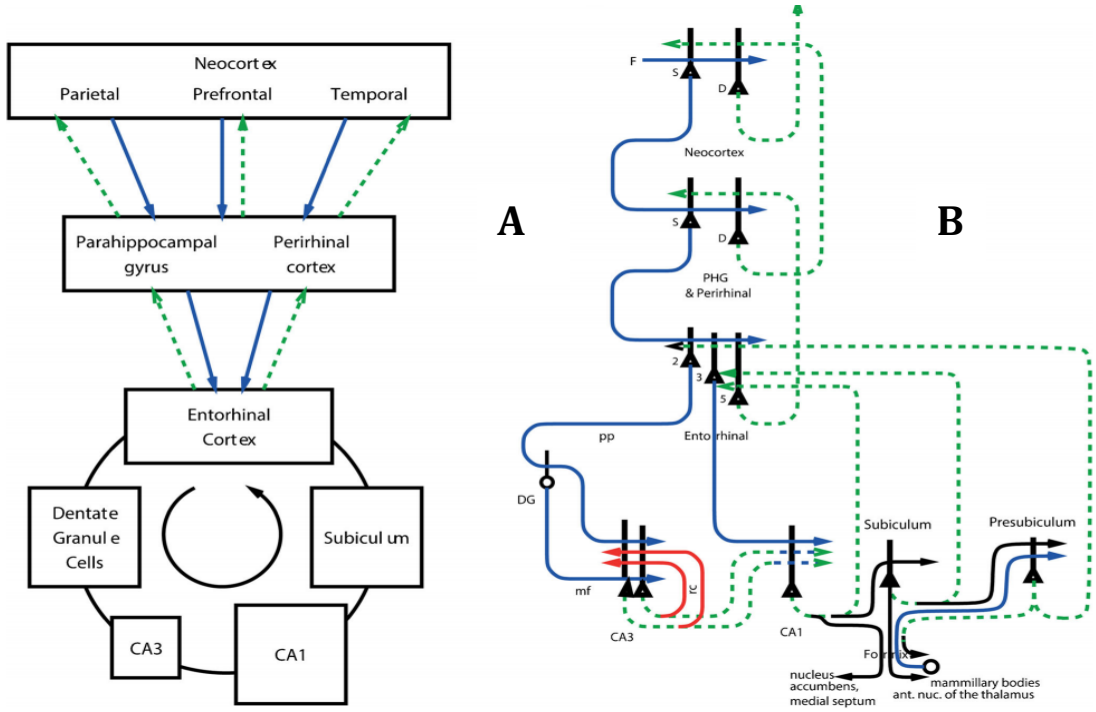

Fig. 1. Schematic representation of forward connections (blue lines) from areas of the cerebral association neocortex via the parahippocampal gyrus and perirhinal cortex and entorhinal cortex to the hippocampus and

backprojections (dashed green lines) via the hippocampal CA1 pyramidal cells, subiculum, and parahippocampal gyrus to the neocortex. A - Block diagram. B - Detailed representation of some of the principal excitatory neurons in the pathways. The CA3 recurrent collateral connections are shown in red (D deep pyramidal cells, DG - dentate granule cells, F - forward inputs to areas of the association cortex from preceding cortical areas in the hierarchy, mf mossy fibers, PHG - parahippocampal gyrus, and perirhinal cortex, pp - perforant path, rc - recurrent collateral of the CA3 hippocampal pyramidal cells, S -superficial pyramidal cells, 2 - pyramidal cells in layer II of the entorhinal cortex, 3 - pyramidal cells in layer III of the entorhinal cortex, dendrites (thick lines above the cell bodies) (adapted from Rolls, 2016).

4.1 Backprojections to the neocortex

A theory was introduced which proposed that CA3 neurons operate as an autoassociation memory for storing episodic memories including those about object and place by performing pattern separation and thus the mossy fibers could be able to set up different representations for each memory, which should be later stored in the cells of the CA3 field. This theory also described CA1 cells operating as a "re-coder" of (involves recoding of the original input event into an information-rich pattern of firing of a few hippocampal neurons) the information recalled from CA3 cells to a partial memory cue, the recalled information would thus be represented more efficiently to enable recall, via the backprojection synapses, of neocortical areas activity similar to the one present during the original episode (Rolls, 1989, 1996, 2016). Backprojections to the neocortex could provide information retrieval from the hippocampus to other brain areas. A computational theory suggests that the modifiable connections from the CA3 neurons to CA1 neurons via the Schaffer collaterals are the key to producing the whole episode in CA3 to CA1, which would later activate layer V cells in the entorhinal cortex. These neurons would via their backprojections originally providing inputs to the hippocampus, terminate in the superficial layers of those neocortical areas, where synapses would arise onto the distal parts of the cortical pyramidal cell dendrites. Recalling of previous episodic events via the backprojections may provide important information to the neocortex by creating new structured representations in the multimodal (e.g., the superior temporal sulcus) and unimodal (e.g., inferior temporal visual cortex) association cortical areas. (Rolls, 1989; 2016). This CA1 backprojection system involves a large number of connections and thus is likely to be necessary for allowing many memories to be retrieved from the hippocampus back to the neocortex. Once a memory has been retrieved to the neocortex, the neocortex then mediates a way for the hippocampal function to influence behavior (Rolls, 2016). These CA1 backprojections via the entorhinal cortex to the parahippocampal gyrus, which eventually end in the neocortex (parietal cortex) might allow spatial representations to be retrieved (Rolls, 2016).

As already mentioned above, there are also more direct hippocampal CA1, subicular, and entorhinal connections to the PFC (Jay & Witter, 1991), which possibly allow the hippocampus to provide inputs to PFC networks that are involved in planning actions (Deco & Rolls, 2003, 2005). Setting up a new episodic memory is another highly important mechanism. The CA3 synapses are modified in the course of an episode and an activity pattern is produced on the backprojecting synapses through CA1 neurons

and the subiculum to the entorhinal cortex. The backprojecting synapses from active backprojection axons onto pyramidal cells are then being activated by the forward inputs to the entorhinal cortex and are associatively modified. Preceding stages of the neocortex, i.e., in the parahippocampal gyrus/perirhinal cortex stage, probably perform a similar process (Rolls, 2016).

4.2 Neural reinstatement

The neural pattern reinstatement is being recognized as a hallmark of successful memory retrieval. A model was proposed by Teyler and colleagues suggesting a bidirectional connection from the hippocampus to the neocortex. This theory adds that the hippocampus acts as a memory "index" of patterns. During encoding of an event, a pattern of activation in the neocortex is produced. The neocortical cells may later activate a group of hippocampal cells, which become interconnected and then act as a retrieval index for the original pattern of cortical activation. Reactivating this index during retrieval leads to the reinstation of that pattern by the hippocampus (Teyler & DiScenna, 1986; Teyler & Rudy, 2007). The memory as reinstatement (MAR) model by Davachi and Danker hypothesized that what differentiates the two patterns is that the hippocampal neural pattern comprises the critical connections between representations that allow the cortical neural pattern to be accessed later and be attributed to a particular time and place - an episodic memory. Therefore, without the hippocampal neural pattern, it would be difficult to recover the specific cortical neural pattern associated with a prior event or experience. This model assumes that subsequent reinstatement is mediated by pattern completion, which is triggered by a retrieval cue. The pattern completion ensures that a part or the entire hippocampal pattern established during encoding and subsequently strengthened becomes reinstated. This reinstatement then possibly reinstates aspects of the cortical pattern, resulting in the concurrent reactivation of cortical regions that were active during the particular past experience (Davachi & Danker, 2013). In summary, these theoretical models of hippocampal function in memory propose that hippocampal pattern completion could be crucial to reactivate and bring back to mind information associated with an experience from the past and thus, mediate cortical reinstatement during remembering (Teyler & DiScenna, 1986; Teyler & Rudy, 2007; Davachi & Danker, 2013).

There are multivariate functional magnetic resonance imaging (fMRI) analyses, used for measuring the similarity of activation patterns elicited during memory encoding and memory retrieval, supporting the idea that the retrieval of episodic memories involves reinstating patterns of cortical activity engaged during encoding, but also demonstrating that reinstatement is not only restricted to occurrences in which subjects reportedly retrieve specific episodic information, but it rather appears in situations where recognition is indicated as being guided solely by a strong feeling of familiarity or knowing, however at a lower magnitude (Johnson et al., 2009). Encoding-retrieval similarity analyses, also used to measure the reinstatement of episodic memories, provide evidence for the reinstatement of unique memories, both in the hippocampus, specifically the right CA1 field, and in the perirhinal cortex as well (Tompary et al., 2016).

4.3 Neural oscillations

In the brain cortex as well as in the hippocampus the cooperation of excitatory principal cells and inhibitory interneurons together create firing neurons, which can also be inhibited and can form rhythmic firing patterns depending on the temporal and spatial distribution of inhibition (Buzsáki, 2006). The theta oscillation is a rhythm that appears at ~3–10 Hz in rodents and is thought to play a crucial role in spatial navigation and memory and appears to be the most prominent clocking mechanism in the forebrain (Buzsáki, 2002, 2006; Hasselmo et al., 2002). The first experiments showing that theta oscillations depend on ongoing behaviour were carried out by Grastyán et al. (1959). As for hippocampal theta oscillation in humans, further research regarding their function is needed, however recent studies suggest that human hippocampal theta oscillations are more than just a slower and noisier analog of the single theta oscillation seen in rodents, but instead exist in multiple forms. The researchers identified high (~8 Hz) theta oscillations in the posterior hippocampus, that varied their frequency with the speed of movement during virtual navigation, and slower (~3 Hz) hippocampal theta oscillations with distinct functional and anatomical properties (Goyal et al., 2020).

There is evidence that hippocampal theta oscillation is related to the encoding and retrieval of new episodic information. Through a certain form of synaptic potentiation (synaptic strengthening) optimal at the theta frequency information could be encoded in memory and later retrieved (Givens, 1996). These oscillations are not a specific monolithic clock signal, instead are rather created by a heterogeneous grouping of transmembrane currents reflecting layer-specific processing, that can be modulated by extrahippocampal inputs or differential processes within the hippocampus (Montgomery et al., 2009).

The model proposed by Hasselmo and colleagues suggests that oscillatory changes in the magnitude of synaptic transmission, long-term potentiation, and postsynaptic depolarization during theta rhythm could possibly cause transitions between two functional phases in each theta cycle - the encoding and the retrieval phase. The first encoding phase supposedly includes activation of cells in regions CA3 and CA1 by a dominant entorhinal input. During this process, excitatory synapses arising from CA3 decrease transmission but also show enhanced long-term potentiation to form associations between sensory events. On the other hand, in the retrieval phase, entorhinal input is relatively weak, however, it still brings retrieval cues into the memory network. Excitatory synapses arising from CA3 show strong transmission and thus allow retrieval of the previously learned associations during this phase. An important aspect of this stage is that long-term potentiation must be absent, to prevent encoding of the retrieval activity to happen. This allows the pure strengthening of relevant synapses. The retrieval does not occur without a prior representation. The model points out that these two phases appear continuously within each 100-300 msec cycle of theta rhythm (Hasselmo et al., 2002). There is evidence that theta rhythms also coordinate hippocampal–prefrontal interactions in spatial memory and disruption of such complex communication may possibly generate behavioral impairments (Jones & Wilson, 2005).

In addition to theta oscillations, it is worth mentioning gamma oscillations, which are thought to play an important role in memory function by facilitating interactions between brain regions. Study of gamma oscillations in CA1, which had two distinct frequency components - a slow gamma range (25–50 Hz) and a fast gamma range (65–140 Hz), indicates that fast gamma enhances transmission from the medial entorhinal cortex to CA1 and that slow gamma promotes signaling from CA3 to CA1 (Colgin et al., 2009). Montgomery and Buzsáki hypothesized that gamma oscillations may serve as a physiological mechanism by which CA3 output can coordinate CA1 activity to support retrieval of hippocampus-dependent memories. This proposition was based on their findings signifying that gamma oscillations can dynamically coordinate hippocampal networks according to behavioral demands (Montgomery & Buzsáki, 2007). As mentioned above, the separation of inputs to CA1 on different phases of theta is probably important for avoiding re-encoding of previously stored memories and allows pure strengthening of relevant synapses distinguishing the ongoing experiences from internally evoked memories (Hasselmo et al., 2002). The results presented by Colgin and colleagues raise the possibility that slow and fast gamma may be also important in this separation of inputs by filtering out improperly timed signals from one afferent and at the same time facilitating the transfer of coherent activity from another (Colgin et al., 2009).

There is an orthogonal arrangement of gamma and theta rhythm-generating microcircuits in the CA3 field of the hippocampus. Theta frequency oscillations are the dominant network activity along the long axis of the hippocampus and are interconnected via CA3 pyramidal cells and oriens and lacunosum-moleculare interneurons, which are providing a theta-frequency patterned output to distal further-reaching dendritic regions of pyramidal cells along the long axis of the hippocampus. Gamma-band oscillations, on the other hand, are observed largely within the transverse axis of the hippocampus, meaning that gamma rhythms are more prevalent in the short-range connections via the activity of local interneurons (Gloveli et al., 2005). Findings obtained very recently demonstrate that distinct gamma-frequency-specific communication between medial entorhinal cortex, lateral entorhinal cortex, and hippocampal cell assemblies are crucial for routing task-relevant information and support of specific aspects of learning. Specific projected gamma patterns dynamically engage functionally related assemblies of cells across the brain in a task-specific manner (Fernández-Ruiz et al., 2021).

It is also believed that there are factors that can disrupt network stability, such as extrahippocampal input frequency or potentiated *N*-Methyl-D-aspartate synapses (Kunec et al., 2005). Specific methods and instruments are used to measure rhythmic neural activity. Studies concerning an animal model may use multi-unit recording and local field potentials (LFPs). Intracranial electroencephalography (iEEG) is often used in human models, mostly for patients with epilepsy, as well as scalp electroencephalography (EEG) and magnetoencephalography (Nyhus & Curran, 2010).

4.4 Engram reactivation theory

Richard Semon (1904) was the first to introduce the term “engram” describing it as the neural substrate (physical memory trace) for storing and later recalling memories. Semon suggested that the creation of an engram begins with a specific learning experience activating a population of neurons that persistently chemically or physically changes and eventually becomes an engram; these neurons are then called engram cells. Engram reactivation by various cues present at the time of the experience can possibly induce memory retrieval (reviewed in Tonegawa et al., 2018). Most of the studies on memory engrams in rodents have investigated and focused on contextual fear conditioning, which is the most basic of the conditioning procedures. It involves placing an animal in a novel environment, providing an aversive stimulus, and later removing it (Curzon et al., 2009). Evidence of the role of memory engram cells is provided e.g., by the research of optogenetic activation of hippocampal engram cells that were active during contextual fear conditioning, which produced memory retrieval (Liu et al., 2012).

In addition to the hippocampus, engram cells are distributed in the neocortex as well. In rats, engram cells for remote contextual fear memory were discovered in the PFC (Kitamura et al., 2017) and studies observed a close linear relationship between the hippocampal activity decrease and the activity increase in the ventral mPFC. Therefore, a functional interaction between these two brain regions is assumed (Takashima et al., 2006). Activity-dependent cell labeling technology, which identifies memory engram cells, helped to investigate the nature and dynamics of neocortical and subcortical memory engram cell and their circuits for systems consolidation of memory. Kitamura introduced a concept that neocortical prefrontal memory engram cells, critical for remote contextual fear memory, are rapidly generated during the initial learning stage of that contextual fear conditioning through inputs from the hippocampal–entorhinal cortex network and the basolateral amygdala, a brain region that plays a role in emotional responses e.g., fear. The prefrontal engram cells, with support from hippocampal memory engram cells, become functionally mature with time and the hippocampal engram cells, on the other hand, gradually became silent with time (Kitamura et al., 2017). The memory engram cells in this state are referred to as silent engrams. Silent engram cells are not reactivated by natural cues, however, can be reactivated artificially to acquire their encoded memory (Tonegawa et al., 2018). The difference between silent and active engram cells is that silent cells have relatively few dendritic spines compared to active engram cells. Hippocampus engram cells in an active state and are reactivated during memory recall are proved to be necessary for memory recall (Fig. 2) (Ryan et al., 2015; Roy et al., 2016; Kitamura et al., 2017).

Considerable evidence has emerged that engram cells in the dentate gyrus may play a role in memory retrieval and that spine density restoration in dentate gyrus engram cells contributes to the rescue of long-term memory in early Alzheimer’s disease of mice. This may provide therapeutic value for future approaches that rescue memory in patients with this disease (Roy et al., 2016; Bernier et al., 2017). Research of dentate gyrus engram cells' structural plasticity demonstrated some specific

properties as increased dendritic spine density and higher synaptic strength in dentate gyrus engram cells in contrast to non-engram cells. Findings of this research propose that the role of synaptic strength may be important for providing natural retrieval cues with efficient access to the soma of engram cells for their reactivation and consequently the retrieval (Ryan et al., 2015).

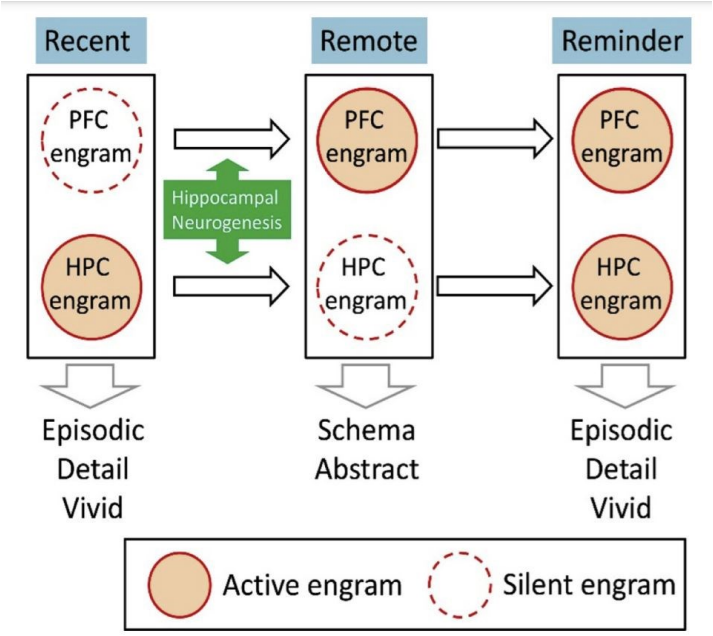

Fig. 2. Scheme of memory engram cells in the hippocampus and PFC. In the recent memory period, hippocampal (HPC) engram cells are active, and PFC engram cells are silent. By activating HPC engram cells, episodic memory retrieval occurs. Adult hippocampal neurogenesis facilitates the transition of HPC engram cells from active to silent, and also simultaneously facilitates the transition of PFC engram cells from silent to active for the formation of remote memory. As for remote memory formation, the hippocampal neurogenesis modulates the change of HPC engram state from active to silent as well as facilitates PFC engram cell state from silent to active (adapted from Terranova et al., 2019).

5 Clinical significance and imaging methods

The case of patient H.M. showed that bilateral damage to the hippocampus executed to treat epilepsy caused an inability to remember recent events, which happened since the hippocampal damage. The episode memory that occurred before the hippocampal damage including semantic and skill memory however remained nearly unimpaired (Scoville & Milner, 1957; Corkin, 2002). Hippocampal damage also causes impairment in temporal order memory regarding places or objects (Hoge & Kesner, 2007; Hunsaker & Kesner, 2008). Hippocampal lesions may also cause relative impairment for memory for temporal distances for the odors, yet the rats are still possibly able to discriminate between the odors (Kesner et al., 2002; Fortin et al., 2002). Hippocampus and its related areas are the earliest and most critically affected structures in several neuropsychiatric disorders such as Alzheimer's disease, epilepsy, schizophrenia, etc.

Alzheimer's disease is linked to progressive accumulation of abnormal proteins in the brain as amyloid-β and hyperphosphorylated tau protein, which eventually leads to progressive synaptic, neuronal, and axonal destruction and damage. Associated changes may be asymptomatic many years before first symptoms appear (up to stage 6 out of 10). Alzheimer's disease also depends on several dynamic processes. For example, the selective vulnerability of neurons, as the hippocampal region is

always widely affected in aging. Aging initiates the degeneration process, which is intensified by a general brain dysfunction of β-Amyloid precursor protein (loss of function or neurotoxicity of amyloid-β). Another variable is the hierarchical collapse of subsets of neurons, which probably has its own dynamic (Delacourte et al., 1999). Structural and functional changes in the hippocampal region contribute to memory impairment (Reitz et al., 2009) and are associated with dementia (Tomlinson et al., 1970).

Schizophrenia is another neurological disorder whose symptoms comprise psychosis, like hallucinations and other delusions, and neurocognitive deficits as attentional, memory, and executive deficits (Crow, 1980, 1981; Cornblatt et al., 1985). Functional-imaging studies have provided evidence from animal models of the hippocampal overactivity caused by reduced GABAergic inhibition (disinhibition) of hippocampal neuronal firing as the main characteristic of schizophrenia pathophysiology (Friston et al., 1992; Malaspina et al., 2004). Schobel reported that hippocampal overactivity, as indicated by elevated cerebral blood flow in the hippocampus of schizophrenia patients particularly in the CA1 region, predicts progression from a prodromal state to schizophrenia and is closely related to psychotic symptoms (Schobel et al., 2009).

Hippocampal sclerosis is a neuropathological defect that is characterized by neuronal loss and gliosis in the CA1 subfield and subiculum of the hippocampus. It is a frequent pathologic finding in elderly subjects with community-based dementia. Hippocampal sclerosis shows similar initial symptoms and rates of dementia progression as patients with Alzheimer's disease and therefore are commonly misclassified and confused with each other (Leverenz et al., 2002). Hippocampal sclerosis is closely associated with long-standing temporal lobe epilepsy (Margerison & Corsellis, 1966). Mechanism of hippocampal sclerosis in epilepsy could be caused by the development of uncontrolled local hippocampal inflammation and blood-brain barrier damage (Yang et al., 2010).

Epilepsy contains numerous different diseases and conditions that are the reason why it has been traditionally referred to as a disorder or a family of disorders emphasizing a functional disturbance, which is not necessarily lasting, rather than a disease, which is usually a more lasting disturbance of normal function. However, the International League Against Epilepsy and the International Bureau for Epilepsy have recently agreed that epilepsy is best considered to be a disease, also because of its serious nature (Fisher et al., 2014). Epilepsy is a brain disorder characterized predominantly by an enduring predisposition to generate epileptic seizures, transient occurrences of signs and symptoms due to abnormal excessive or synchronous neuronal activity, and is also characterized by the neurobiological, cognitive, psychological, and social consequences of this condition. This definition requires the occurrence of at least one epileptic seizure (Fisher et al., 2005). Experimental data indicate that the hippocampus proper participates in the semantic processing of complex visual stimuli. This participation can be possibly impaired by temporal lobe epilepsy. The nonepileptic hippocampus proper discriminates between pictures of real and nonsense objects and then responds differentially to both kinds of stimuli.

The epileptic hippocampus, in comparison, did not differentiate between the two classes of complex visual stimuli (Vannucci et al., 2003).

6 Discussion

This thesis investigated the hippocampal and neocortical contributions to memory formation during retrieval. Although the fundamental role of the hippocampus and neocortex in the retrieval of declarative memories has been presented, further research is needed to characterize these processes in more detail, specifying how the interactions between prefrontal and hippocampal regions differ during cognitive operations such as retrieval cue specification, or maintenance and monitoring of retrieved information.

One of the questions that still need to be answered is what happens with memories in the long term (referring to memory consolidation). It is still a matter of debate as different studies show decreased (Takashima et al., 2006) or increased (Addis et al., 2004) hippocampal activity over time after memory consolidation and thus oppose each other. Another important question already mentioned in the Introduction is whether human declarative memory relies on the same neural processes as spatial memory and should be considered as another declarative memory subtype? Consequently, how is the theta oscillation observed in spatial memory related to the memory retrieval of other declarative memory subtypes?

With respect to engram cell reactivation theories, it should be more closely described how information is stored in an engram in terms of memory quality or strength. Interactions between engram cells and their changes over time also require more attention. In the future, research on rodent engram cells and other retrieval mechanisms might provide crucial findings to understand how information is acquired, stored, and retrieved in the human brain and therefore has the potential to help with the treatment of human memory disorders. The selective rescue of spine density in engram cells may lead to e.g., an effective strategy for treating memory impairment in Alzheimer's disease (Roy et al., 2016). Further research on theta and gamma oscillation in humans is also lacking.

Next, the areas commonly activated in memory retrieval were described; however, more theoretical research is needed, as there are many different views between many cognitive models and empirical observations, as well as much ambiguity about terminology.

The development of low-invasive or non-invasive technology may allow new human therapies. Nowadays, human functional neuroimaging techniques provide a tool to link neural level descriptions of brain function and cognition. Neuroimaging techniques, i.e., magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), and positron emission tomography (PET), can show abnormalities of the hippocampus, allow resolution of sufficient quality to provide information about the abnormal hippocampal structure and disease state (Heckers, 2001). Optogenetic and chemogenetic memory studies offer defined neuroanatomy of the neuronal circuits in the brain and are already used

for example in fear conditioning (Li et al., 2020). These two techniques enable to study and manipulation of specific neuronal populations within brain structures as well as the functional connections between them (Muir et al., 2019). Combining optogenetic or chemogenetic with in vivo imaging techniques, such as fMRI, could provide important new information on the physiological significance of memory circuits, which could help to investigate memory retrieval processes and thus provide important information for understanding the human brain and improving human therapies in the future.

Two-photon excitation laser scanning microscopy (Denk et al., 1990) allows high-resolution optical imaging in scattered tissue. It can be used to visualize neuronal Ca2+ spiking with millisecond-scale timing resolution in the brains of a mouse (Zhang et al., 2019). This method still has its limitation, however, it has also the potential to significantly support the study on molecular mechanisms of engram cells, etc.

7 Conclusion

There is a wide agreement supported by numerous studies providing evidence that interactions between neocortex and hippocampus are key for successful memory retrieval. Our understanding of the interplay between these regions is still at an early stage. This thesis should serve mainly as a general overview and help with the general orientation between the different structures and mechanisms that contribute to memory retrieval. The understanding of intrinsic connectivity of the hippocampal regions, especially the trisynaptic pathway, is undoubtedly crucial, as every region provides an important aspect contributing to the retrieval of memories. The linkage of the hippocampus to the neocortex is supported by numerous studies and the role of the PFC and PPC is emphasized. Different regions of the PFC are likely to provide different functions during the retrieval phase, such as the controlled cue specification during retrieval attempts, the maintenance of retrieved representations, the monitoring operations, and the evaluation of representations retrieved from memory. The role of an engram in memory retrieval was described, showing again a close relationship between hippocampal and prefrontal engram cells. Pattern reinstatement is also considered a pivotal mechanism of the hippocampal-neocortical interplay. During encoding, a pattern of activation in the neocortex is produced. The neocortical cells may later activate a group of hippocampal cells that act as a retrieval index for the original pattern of cortical activation. Reactivating of this index during retrieval leads to the reinstation of that pattern by the hippocampus. Theta and gamma rhythms' contribution to encoding and retrieval activity was presented. Oscillatory changes in the magnitude of synaptic transmission, long-term potentiation, and postsynaptic depolarization during theta rhythm could possibly cause transitions between the encoding and the retrieval phase of each theta cycle. The importance of the hippocampus in memory is evident and the consequences of its impairment are apparent in several serious diseases.

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